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DB=PGPB,USPT; PLUR=YES; OP=AND			
L9	l3 near8 l4	42	L9
L8	l5 and l7	70	L8
L7	fabry adj disease	637	L7
L6	farbry adj disease	2	L6
L5	l3 and L4	162	L5
L4	enzyme adj replacement adj therapy	294	L4
L3	gene adj therapy	27628	L3
L2	6458574.pn.	1	L2
L1	6083725.pn.	1	L1

END OF SEARCH HISTORY

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Search Results - Record(s) 22 through 41 of 42 returned.

☐ 22. 20010036454. 15 Feb 01. 01 Nov 01. Genetic modification of the lung as a portal for gene delivery. Li, Chester, et al. 424/93.21; 424/43 514/44 A61K048/00 A61L009/04 A61K009/00.

☑ 23. 20010031741. 06 Feb 01. 18 Oct 01. Methods for treatment of lysosomal storage diseases. Ziegler, Robin, et al. 514/44; 424/94.61 514/102 A61K048/00 A61K038/47 A61K031/663.

☐ 24. 6774135. 10 Aug 01; 10 Aug 04. Method of enhancing lysosomal .alpha.-galactosidase A. Fan; Jian-Qiang, et al. 514/315; 435/208 514/277 514/281 514/317 546/219. A61K031/445 A61K031/435 C07D211/40 C12N009/40.

☐ 25. 6759387. 30 Jul 02; 06 Jul 04. Compositions and methods for enhancing drug delivery across and into epithelial tissues. Rothbard; Jonathan B., et al. 514/2; 514/12 514/13 514/14 514/15 514/16 514/17 514/254.07 514/291 514/383 514/399 540/461 544/366 548/266.6 548/342.5. A61K031/436 A61K031/496 A61K038/04 A61K038/16.

☐ 26. 6730293. 24 Aug 00; 04 May 04. Compositions and methods for treating inflammatory diseases of the skin. Rothbard; Jonathan B., et al. 424/78.05; 424/78.17 424/78.37 525/54.11. A61K031/765 A61K038/03 A61K038/16 C07K007/00 C07K014/00.

☐ 27. 6696272. 02 Jun 00; 24 Feb 04. Products and methods for gaucher disease therapy. Mahuran; Don J., et al. 435/69.1; 424/93.21 435/320.1 435/325 435/455 536/23.2 536/23.5. C12P021/06 C07H021/04 C12N015/00 C12N015/63 A01N063/00.

☐ 28. 6669951. 23 Feb 01; 30 Dec 03. Compositions and methods for enhancing drug delivery across and into epithelial tissues. Rothbard; Jonathan B., et al. 424/436; 514/11 514/16 514/169 514/2 514/634 514/636 530/300 530/329 564/236 564/243. A61K009/02 A61K038/03 A61K038/08 A61K038/13 A61K047/42.

☐ 29. 6605275. 17 May 95; 12 Aug 03. Isolation and preservation of fetal and neonatal hematopoietic stem and progenitor cells of the blood. Boyse; Edward A., et al. 424/93.7; 424/529 424/583. C12N005/00.

☐ 30. 6593292. 24 Aug 00; 15 Jul 03. Compositions and methods for enhancing drug delivery across and into epithelial tissues. Rothbard; Jonathan B., et al. 514/2; 514/11 514/12 514/15 514/159 514/16 514/169 514/17 514/254.07 514/263.31 514/291 514/423 514/456 514/458 514/634 514/635 514/636 530/300 530/321 530/328 530/329 530/330 544/366. A61K031/496 A61K038/13 A61K047/16 A61K047/42.

☐ 31. 6569427. 16 May 95; 27 May 03. Isolation and preservation of fetal and neonatal hematopoietic stem and progenitor cells of the blood. Boyse; Edward A., et al. 424/93.7; 424/529 424/530 424/531 435/372. C12N005/00.

☐ 32. 6566099. 27 Jan 00; 20 May 03. Nucleic acid encoding a chimeric polypeptide. Selden; Richard F., et al. 435/69.8; 435/200 435/207 435/366 435/455 530/350 536/23.1 536/23.5 536/24.1. C12P021/04 C12N009/24 C07K001/00 C07H021/02 C07H021/04.

h e b b cg b cc e

☐ 33. 6495663. 14 Sep 99; 17 Dec 02. Method and composition for enhancing transport across biological membranes. Rothbard; Jonathan B., et al. 530/329; 530/324 530/325 530/326 530/327 530/328. C07K007/00.

☐ 34. 6461645. 16 May 90; 08 Oct 02. Isolation and preservation of fetal and neonatal hematopoietic stem and progenitor cells of the blood. Boyse; Edward A., et al. 424/529; 424/93.7 435/2. A61K035/14.

☐ 35. 6395884. 06 Apr 00; 28 May 02. Therapy for .alpha.-galactosidase a deficiency. Selden; Richard F., et al. 530/417; 435/455 435/6 435/69.1 435/69.8 435/70.1 530/350. C07K001/00 C07K014/00 C12N015/63 C12P021/06 C12P021/04.

☐ 36. 6306993. 21 May 98; 23 Oct 01. Method and composition for enhancing transport across biological membranes. Rothbard; Jonathan B., et al. 526/304; 514/2 514/449 514/549. A61K031/765 A61K038/08 A61K031/335 A61K031/22 A61K038/10.

☐ 37. 6274597. 01 Jun 98; 14 Aug 01. Method of enhancing lysosomal .alpha.-Galactosidase A. Fan; Jian-Qiang, et al. 514/315;. A61K031/445.

☐ 38. 6083725. 12 Sep 97; 04 Jul 00. Tranfected human cells expressing human .alpha.-galactosidase A protein. Selden; Richard F., et al. 435/69.8; 435/208 435/320.1 435/366 435/367 435/368 435/369 435/370 435/371 435/372 435/372.1 435/372.2 435/372.3 435/455 536/23.2 536/23.4. C12N005/10 C12N005/08 C12N009/40 C12P021/02.

☐ 39. 5798366. 13 Jan 97; 25 Aug 98. Method for treatment of CNS-involved lysosomal storage diseases. Platt; Frances M., et al. 514/315;. A61K031/445.

☐ 40. 5720720. 15 Mar 96; 24 Feb 98. Convection-enhanced drug delivery. Laske; Douglas W., et al. 604/500; 604/21. A61M031/00.

☐ 41. 5192553. 10 Nov 88; 09 Mar 93. Isolation and preservation of fetal and neonatal hematopoietic stem and progenitor cells of the blood and methods of therapeutic use. Boyse; Edward A., et al. 424/529; 424/93.21 435/2 435/374 435/378 435/455. A61K035/50 A61K035/14.

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Terms	Documents
L3 near8 L4	42

Prev Page Next Page Go to Doc#

h e b b cg b cc e

Generate Collection Print

Search Results - Record(s) 61 through 70 of 70 returned.

☐ 61. 6566099. 27 Jan 00; 20 May 03. Nucleic acid encoding a chimeric polypeptide. Selden; Richard F., et al. 435/69.8; 435/200 435/207 435/366 435/455 530/350 536/23.1 536/23.5 536/24.1. C12P021/04 C12N009/24 C07K001/00 C07H021/02 C07H021/04.

☑ 62. 6458574. 11 Mar 99; 01 Oct 02. Treatment of a .alpha.-galactosidase a deficiency. Selden; Richard F, et al. 435/208; 424/94.1 424/94.61 435/183 435/193 536/23.1 536/23.2 536/23.4. C12N009/40 A61K038/43.

☐ 63. 6395884. 06 Apr 00; 28 May 02. Therapy for .alpha.-galactosidase a deficiency. Selden; Richard F., et al. 530/417; 435/455 435/6 435/69.1 435/69.8 435/70.1 530/350. C07K001/00 C07K014/00 C12N015/63 C12P021/06 C12P021/04.

☐ 64. 6328958. 27 Aug 99; 11 Dec 01. Deleted adenovirus vectors and methods of making and administering the same. Amalfitano; Andrea, et al. 424/93.2; 435/320.1 435/455 435/91.4 514/44. A61K048/00 C12N015/88.

☐ 65. 6274597. 01 Jun 98; 14 Aug 01. Method of enhancing lysosomal .alpha.-Galactosidase A. Fan; Jian-Qiang, et al. 514/315;. A61K031/445.

☐ 66. 6210666. 21 Oct 98; 03 Apr 01. Truncated .alpha.-galactosidase A to treat fabry disease. Miyamura; Nobuhiro. 424/94.61; 435/200 435/208 530/350. A61K038/47 C12N009/40.

☑ 67. 6083725. 12 Sep 97; 04 Jul 00. Tranfected human cells expressing human .alpha.-galactosidase A protein. Selden; Richard F., et al. 435/69.8; 435/208 435/320.1 435/366 435/367 435/368 435/369 435/370 435/371 435/372 435/372.1 435/372.2 435/372.3 435/455 536/23.2 536/23.4. C12N005/10 C12N005/08 C12N009/40 C12P021/02.

☐ 68. 6066626. 29 Oct 98; 23 May 00. Compositions and method for treating lysosomal storage disease. Yew; Nelson S., et al. 514/44; 424/93.1 424/94.61 435/183 435/208 435/320.1 435/325. A01N043/04.

☐ 69. 5798366. 13 Jan 97; 25 Aug 98. Method for treatment of CNS-involved lysosomal storage diseases. Platt; Frances M., et al. 514/315;. A61K031/445.

☐ 70. 4866042. 18 Nov 87; 12 Sep 89. Method for the delivery of genetic material across the blood brain barrier. Neuwelt; Edward A.. 424/93.2; 514/44. A61K035/76 A61K039/00 A61K039/21 A61K045/05.

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Terms	Documents
L5 and L7	70

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09/884,526

FILE 'MEDLINE, CAPLUS, BIOSIS, SCISEARCH' ENTERED AT 17:05:31 ON 24 JAN 2005

L9 27670 S (ENZYME OR PROTEIN)(5A)THERAPY
L10 113393 S GENE(W)THERAPY
L11 5882 S L1 AND L2
L12 3243 S FABRY(W)DISEASE
L13 4675 S L1(8A)L2
L14 33 S L13 AND L12
L15 23 DUP REM L14 (10 DUPLICATES REMOVED)
L16 53 S L1(8A)COMBIN?(6A)L2
L17 32 DUP REM L16 (21 DUPLICATES REMOVED)
L18 3 S L17 AND L12

=> d au ti so pi ab 1-3 l18

L18 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN
IN Cheng, Seng H.; Meeker, David
TI **Combined enzyme** replacement, **gene therapy** and small molecule therapy for lysosomal storage diseases
SO U.S. Pat. Appl. Publ., 35 pp., Cont.-in-part of U.S. Ser. No. 884,526.
CODEN: USXXCO

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2004204379	A1	20041014	US 2004-758773	20040116
US 2002095135	A1	20020718	US 2001-884526	20010619

AB This invention provides various **combinations** of **enzyme** replacement **therapy**, **gene therapy**, and small mol. therapy for the treatment of lysosomal storage diseases. Thus, in a mouse **Fabry disease** model, substrate deprivation therapy with deoxynorjirimycin derivative AMP-DNJ and D-threo-1-(3',4'-methylenedioxy)phenyl-2-palmitoylamino-3-pyrrolidino-1-propanol reduced reaccumulation of globotriaosylceramide GL3 following its reduction by enzyme replacement therapy with α-galactosidase A. Addnl., adeno-associated virus AAV2 expression vectors containing the α-galactosidase A gene fused to the liver-specific DC190 promoter were prepared The DC190 promoter consists of the human serum albumin promoter to which 2 copies of the human prothrombin enhancer were appended. Fabry mice administered this vector developed an immune tolerance to the enzyme.

L18 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN
IN Fan, Jian-Quiang
TI Combination therapy for treating protein deficiencies
SO PCT Int. Appl., 40 pp.
CODEN: PIXXD2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004074450	A2	20040902	WO 2004-US4909	20040218
WO 2004074450	C1	20041104		

W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ, MZ, NA, NI

RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2004219132 A1 20041104 US 2004-781356 20040217

AB This application provides methods of improving gene therapy by combining gene therapy with active site-specific chaperones (ASSCs). The ASSC

increases the stability and efficiency of the protein encoded by the recombinant gene that is administered. Gene therapy for α-galactosidase A, deficient in **Fabry disease**, uses a reversible competitive inhibitor such as 1-deoxygalactonojirimycin as ASSC.

L18 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN
IN Meeker, David; Cheng, Seng H.
TI **Combination enzyme** replacement, **gene therapy** and small molecule therapy for lysosomal storage diseases
SO PCT Int. Appl., 45 pp.
CODEN: PIXXD2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001097829	A2	20011227	WO 2001-US19579	20010619
WO 2001097829	A3	20021227		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AB This invention provides various **combinations** of **enzyme** replacement **therapy**, **gene therapy**, and small mol. therapy for the treatment of lysosomal storage diseases. Therapy include α-galactosidase A enzyme , deoxynorjirimycin derivs. (small mols.) for **Fabry disease**.

=> d au ti so 20-32 l17

L17 ANSWER 20 OF 32 CAPLUS COPYRIGHT 2005 ACS on STN
AU Chen, Bing; Timiryasova, Tatyana M.; Andres, Melba L.; Kajioka, Eric H.; Dutta-Roy, Radha; Gridley, Daila S.; Fodor, Istvan
TI Evaluation of combined vaccinia virus-mediated antitumor gene therapy with p53, IL-2, and IL-12 in a glioma model
SO Cancer Gene Therapy (2000), 7(11), 1437-1447
CODEN: CGTHEG; ISSN: 0929-1903

L17 ANSWER 21 OF 32 MEDLINE on STN DUPLICATE 7
AU Greco O; Folkes L K; Wardman P; Tozer G M; Dachs G U
TI Development of a novel **enzyme**/prodrug **combination** for **gene therapy** of cancer: horseradish peroxidase/indole-3-acetic acid.
SO Cancer gene therapy, (2000 Nov) 7 (11) 1414-20.
Journal code: 9432230. ISSN: 0929-1903.

L17 ANSWER 22 OF 32 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation. on STN
AU Springer C J
TI Suicide **gene therapy** with new **enzyme**/prodrug **combinations**.
SO HUMAN GENE THERAPY, (20 MAR 1999) Vol. 10, No. 5, pp. 845-845.
Publisher: MARY ANN LIEBERT INC PUBL, 2 MADISON AVENUE, LARCHMONT, NY 10538.
ISSN: 1043-0342.

L17 ANSWER 23 OF 32 CAPLUS COPYRIGHT 2005 ACS on STN
AU Marveggio, S.; Raic, S.; Pongracic, M.; Mintas, M.; Pilger, B.; Wurth, C.; Folkers, G.; Scapozza, L.
TI 9-(2-Hydroxypropyl)adenine: a novel fraudulent substrate of HSV1-thymidine

kinase. An interdisciplinary study
SO Proceedings of ECSOC-1: The First International Electronic Conference on Synthetic Organic Chemistry; [and] Proceedings of ECSOC-2: The Second International Electronic Conference on Synthetic Organic Chemistry, Sept. 1-30, 1997, 1998 (1999), Meeting Date 1997-1998, 568-577. Editor(s): Lin, Shu-Kun; Pombo-Villar, Esteban. Publisher: Molecular Diversity Preservation International, Basel, Switz.
CODEN: 69ASBO

L17 ANSWER 24 OF 32 CAPLUS COPYRIGHT 2005 ACS on STN
AU Hamstra, Daniel A.; Rice, David J.; Pu, Anthony; Oyedijo, Dotun; Ross, Brian D.; Rehemtulla, Alnawaz
TI Combined radiation and enzyme/prodrug treatment for head and neck cancer in an orthotopic animal model
SO Radiation Research (1999), 152(5), 499-507
CODEN: RAREAE; ISSN: 0033-7587

L17 ANSWER 25 OF 32 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN
AU Greco, O.; Dachs, G. U.; Wardman, P.; Folkes, L. K.; Chaplin, D. J.
TI Development of an **enzyme**/prodrug **combination** for **gene therapy** of cancer.
SO Proceedings of the American Association for Cancer Research Annual Meeting, (March, 1999) Vol. 40, pp. 478. print.
Meeting Info.: 90th Annual Meeting of the American Association for Cancer Research. Philadelphia, Pennsylvania, USA. April 10-14, 1999. American Association for Cancer Research.
ISSN: 0197-016X.

L17 ANSWER 26 OF 32 CAPLUS COPYRIGHT 2005 ACS on STN
IN Nielsen, Loretta; Horowitz, Jo Ann; Maneval, Daniel C.; Demers, G. William; Rybak, Mary Ellen; Resnick, Gene
TI Combined tumor suppressor gene therapy and chemotherapy in the treatment of neoplasms
SO PCT Int. Appl., 114 pp.
CODEN: PIXXD2

L17 ANSWER 27 OF 32 CAPLUS COPYRIGHT 2005 ACS on STN
IN Blanche, Francis; Cameron, Beatrice; Couder, Michel; Crouzet, Joel
TI Enzyme combinations for producing toxic nucleoside triphosphate analogs for destroying proliferative cells
SO PCT Int. Appl., 76 pp.
CODEN: PIXXD2

L17 ANSWER 28 OF 32 CAPLUS COPYRIGHT 2005 ACS on STN
AU Paillard, Florence
TI Bystander effects in enzyme/prodrug gene therapy
SO Human Gene Therapy (1997), 8(15), 1733-1735
CODEN: HGTHE3; ISSN: 1043-0342

L17 ANSWER 29 OF 32 MEDLINE on STN DUPLICATE 8
AU Green N K; Youngs D J; Neoptolemos J P; Friedlos F; Knox R J; Springer C J; Anlezark G M; Michael N P; Melton R G; Ford M J; Young L S; Kerr D J; Searle P F
TI Sensitization of colorectal and pancreatic cancer cell lines to the prodrug 5-(aziridin-1-yl)-2,4-dinitrobenzamide (CB1954) by retroviral transduction and expression of the E. coli nitroreductase gene.
SO Cancer gene therapy, (1997 Jul-Aug) 4 (4) 229-38.
Journal code: 9432230. ISSN: 0929-1903.

L17 ANSWER 30 OF 32 CAPLUS COPYRIGHT 2005 ACS on STN
IN Tiraby, Gerard; Reynes, Jean-Paul; Tiraby, Michele; Cazaux, Christophe; Drocourt, Daniel
TI Gene therapy by activation of combinations of pyrimidine nucleoside and

nucleobase analogs with fusion proteins of activating enzymes
SO PCT Int. Appl., 65 pp.
CODEN: PIXXD2

L17 ANSWER 31 OF 32 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN
AU GERMANN U A [Reprint author]; GOTTESMAN M M; PASTAN I
TI STABLE EXPRESSION OF A HUMAN MULTIDRUG RESISTANCE-ADENOSINE DEAMINASE FUSION GENE AFTER DNA-MEDIATED TRANSFER INTO HUMAN KB CELLS.
SO Journal of Cell Biology, (1988) Vol. 107, No. 6 PART 3, pp. 326A.
Meeting Info.: JOINT MEETING OF THE AMERICAN SOCIETY FOR CELL BIOLOGY AND THE AMERICAN SOCIETY FOR BIOCHEMISTRY AND MOLECULAR BIOLOGY, SAN FRANCISCO, CALIFORNIA, USA, JANUARY 29-FEBRUARY 2, 1989. J CELL BIOL.
CODEN: JCLBA3. ISSN: 0021-9525.

L17 ANSWER 32 OF 32 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN
AU WILLIAMS D A [Reprint author]; LIM B; APPERLEY J F; ORKIN S H
TI TRANSFER AND EXPRESSION IN-VIVO OF HUMAN ADA COMPLEMENTARY DNA IN MURINE HEMATOPOIETIC CELLS.
SO Journal of Cellular Biochemistry Supplement, (1988) No. 12 PART E, pp. 42.
Meeting Info.: MEETING ON CELL ACTIVATION AND SIGNAL INITIATION: RECEPTOR AND PHOSPHOLIPASE CONTROL OF INOSITOL PHOSPHATE, PAF AND EICOSANOID PRODUCTION HELD AT THE 17TH ANNUAL UCLA (UNIVERSITY OF CALIFORNIA-LOS ANGELES) SYMPOSIA ON MOLECULAR AND CELLULAR BIOLOGY, KEYSTONE, COLORADO, USA, APRIL 17-23, 1988. J CELL BIOCHEM SUPPL.
ISSN: 0733-1959.

=> d pi ab 26 27 l17

L17 ANSWER 26 OF 32 CAPLUS COPYRIGHT 2005 ACS on STN

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9835554	A2	19980820	WO 1998-US3514	19980217
WO 9835554	A3	19981126		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2282683	AA	19980820	CA 1998-2282683	19980217
AU 9864380	A1	19980908	AU 1998-64380	19980217
AU 737621	B2	20010823		
EP 969720	A2	20000112	EP 1998-910038	19980217
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
NZ 337283	A	20010223	NZ 1998-337283	19980217
JP 2001511815	T2	20010814	JP 1998-536033	19980217
BR 9807418	A	20020122	BR 1998-7418	19980217
US 2003060434	A1	20030327	US 1999-311772	19990513
NO 9903943	A	19991015	NO 1999-3943	19990817
US 2003064949	A1	20030403	US 2002-86294	20020228
US 2004235736	A1	20041125	US 2004-824058	20040413

AB In one embodiment, the invention provides methods of treating mammalian cancer or hyperproliferative cells, the method comprising contacting the cells with a tumor suppressor protein or tumor suppressor nucleic acid and also contacting the cells with at least one adjunctive anticancer agent. The invention also provides for a pharmacol. composition comprising a tumor suppressor protein or a tumor suppressor nucleic acid and at least one adjunctive anti-cancer agent, as well as a kit for the treatment of

mammalian cancer or hyperproliferative cells.

L17 ANSWER 27 OF 32 CAPLUS COPYRIGHT 2005 ACS on STN

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9735024	A1	19970925	WO 1997-FR436	19970312
	W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, GH, HU, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	FR 2746016	A1	19970919	FR 1996-3267	19960315
	FR 2746016	B1	19980417		
	CA 2248629	AA	19970925	CA 1997-2248629	19970312
	AU 9721642	A1	19971010	AU 1997-21642	19970312
	AU 732432	B2	20010426		
	EP 910654	A1	19990428	EP 1997-914376	19970312
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, FI				
	BR 9708194	A	19990727	BR 1997-8194	19970312
	JP 2000507814	T2	20000627	JP 1997-533187	19970312
	ZA 9702247	A	19970917	ZA 1997-2247	19970314
	NO 9804132	A	19980908	NO 1998-4132	19980908
	US 6518062	B1	20030211	US 1998-125576	19980910

AB Enzyme combinations useful for destroying cells, particularly proliferative cells, are disclosed. Vectors enabling the intracellular expression and transfer of said enzyme combinations, as well as the therapeutical use thereof, particularly in anti-cancer gene therapy, are also disclosed. Expression plasmids containing herpes simplex virus 1 thymidine kinase gene, Saccharomyces cerevisiae gene GUK1 guanylate kinase, and/or S. cerevisiae gene YNK nucleoside diphosphokinase were prepared Another plasmid encoding a thymidine kinase-guanylate kinase fusion protein was created. Incubation of the 3 enzymes with ganciclovir or acyclovir resulted in production of the nucleoside triphosphate analogs. Phosphorylation of ganciclovir was enhanced 1.8-fold and phosphorylation of acyclovir was enhanced 1.2-fold with the fusion protein (relative to the enzymes employed sep.).

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     FILE 'MEDLINE, CAPLUS, BIOSIS, SCISEARCH' ENTERED AT 16:32:38 ON 24 JAN
     2005
L1         27670 S (ENZYME OR PROTEIN)(5A)THERAPY
L2        113393 S GENE(W)THERAPY
L3          5882 S L1 AND L2
L4          3243 S FABRY(W)DISEASE
L5            67 S L3 AND L4
L6          1665 S ALPHA-GALACTOSIDASE(W)A
L7            45 S L5 AND L6
L8            27 DUP REM L7 (18 DUPLICATES REMOVED)

=> d au ti so pi ab 1-27 l8

L8   ANSWER 1 OF 27  CAPLUS  COPYRIGHT 2005 ACS on STN
IN   Fan, Jian-Quiang
TI   Combination therapy for treating protein deficiencies
SO   PCT Int. Appl., 40 pp.
     CODEN: PIXXD2
     PATENT NO.          KIND   DATE        APPLICATION NO.         DATE
     --------------      ----   --------    --------------------    --------
PI   WO 2004074450        A2    20040902    WO 2004-US4909          20040218
     WO 2004074450        C1    20041104
         W:  AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG,
             BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR,
             CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES,
             ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN,
             IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC,
             LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX,
             MZ, MZ, NA, NI
         RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE,
             BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU,
             MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN,
             GQ, GW, ML, MR, NE, SN, TD, TG, BF, BJ, CF, CG, CI, CM, GA, GN,
             GQ, GW, ML, MR, NE, SN, TD, TG
     US 2004219132         A1    20041104    US 2004-781356          20040217
AB   This application provides methods of improving gene
     therapy by combining gene therapy with active
     site-specific chaperones (ASSCs). The ASSC increases the stability and
     efficiency of the protein encoded by the recombinant gene that is
     administered. Gene therapy for .alpha.-
     galactosidase A, deficient in Fabry
     disease, uses a reversible competitive inhibitor such as
     1-deoxygalactonojirimycin as ASSC.

L8   ANSWER 2 OF 27  CAPLUS  COPYRIGHT 2005 ACS on STN
IN   Cheng, Seng H.; Meeker, David
TI   Combined enzyme replacement, gene therapy
     and small molecule therapy for lysosomal storage diseases
SO   U.S. Pat. Appl. Publ., 35 pp., Cont.-in-part of U.S. Ser. No. 884,526.
     CODEN: USXXCO
     PATENT NO.          KIND   DATE        APPLICATION NO.         DATE
     --------------      ----   --------    --------------------    --------
PI   US 2004204379        A1    20041014    US 2004-758773          20040116
     US 2002095135        A1    20020718    US 2001-884526          20010619
AB   This invention provides various combinations of enzyme
     replacement therapy, gene therapy, and small
     mol. therapy for the treatment of lysosomal storage diseases. Thus, in a
     mouse Fabry disease model, substrate deprivation
     therapy with deoxynorjirimycin derivative AMP-DNJ and D-threo-1-(3',4'-
     methylenedioxy)phenyl-2-palmitoylamino-3-pyrrolidino-1-propanol reduced
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reaccumulation of globotriaosylceramide GL3 following its reduction by **enzyme** replacement **therapy** with .**alpha**.-**galactosidase A**. Addnl., adeno-associated virus AAV2 expression vectors containing the .**alpha**.-**galactosidase A** gene fused to the liver-specific DC190 promoter were prepared The DC190 promoter consists of the human serum albumin promoter to which 2 copies of the human prothrombin enhancer were appended. Fabry mice administered this vector developed an immune tolerance to the enzyme.

L8 ANSWER 3 OF 27 MEDLINE on STN DUPLICATE 1
AU Politei J M; Pagano M A
TI [Peripheral neuropathy in Anderson-**Fabry disease**: its physiology, evaluation and treatment].
Neuropatia periferica en la enfermedad de Anderson-Fabry: fisiopatologia, evaluacion y tratamiento.
SO Revista de neurologia, (2004 May 16-31) 38 (10) 979-83. Ref: 64
Journal code: 7706841. ISSN: 0210-0010.
AB AIMS: The purpose of this study was to review the peripheral neurological aspects of Anderson-**Fabry disease** (AFD). DEVELOPMENT: AFD is a disease caused by lysosomal deposits that was first reported in 1898. This entity has begun to attract renewed interest in recent years because of the progress made in diagnostic techniques and the appearance of **enzyme** replacement **therapy**. This pathological condition is transmitted by recessive inheritance linked to the X chromosome and results from a deficiency of the enzyme **alpha-galactosidase A**, which leads to the accumulation of glycosphingolipids in endothelial and perithelial cells, as well as those of the smooth muscles in blood vessels, the dorsal root ganglia and other structures in the central and peripheral nervous systems. Symptoms during childhood include: neuropathic pain that is predominantly distal in the four limbs (and expresses itself as severe attacks that are often linked to changes in temperature and exercise that interfere with daily activities), hypohidrosis and angiokeratomas. The most serious complications appear during adulthood and include: kidney failure, heart failure and strokes. CONCLUSION: The arrival of **enzyme** replacement **therapy** is the first part of a chain in the treatment of AFD, where **gene therapy** and substrate inhibition therapy are beginning to emerge as real therapeutic alternatives. In spite of all this, at present, the management of painful symptoms is not at all satisfactory for patients and therefore further study and a deeper understanding of the mechanisms involved will allow more specific and effective therapeutic measures to be developed with which to provide patients with greater relief.

L8 ANSWER 4 OF 27 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation. on STN
AU Ziegler R J; Lonning S M; Armentano D; Li C; Souza D W; Cherry M; Ford C; Barbon C M; Desnick R J; Gao G P; Wilson J M; Peluso R; Godwin S; Carter B J; Gregory R J; Wadsworth S C; Cheng S H (Reprint)
TI AAV2 vector harboring a liver-restricted promoter facilitates sustained expression of therapeutic levels of **alpha-galactosidase A** and the induction of immune tolerance in Fabry mice
SO MOLECULAR THERAPY, (FEB 2004) Vol. 9, No. 2, pp. 231-240.
Publisher: ACADEMIC PRESS INC ELSEVIER SCIENCE, 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495 USA.
ISSN: 1525-0016.
AB The successful application of **gene therapy** for the treatment of genetic diseases such as Fabry is reliant on the development of vectors that are safe and that facilitate sustained expression of therapeutic levels of the transgene product. Here, we report that intravenous administration of a recombinant AAV2 vector encoding human **alpha-galactosidase A** under the transcriptional control of a liver-restricted enhancer/promoter (AAV2/DC190-alphagal) generated significantly higher levels of expression

in BALB/c and Fabry mice than could be realized using the ubiquitous CMV promoter (AAV2/CMVHI-alphagal). Moreover, AAV2/DC190-alphagal-mediated hepatic expression of **alpha-galactosidase A** was sustained for 12 months in BALB/c mice and was associated with a significantly reduced immune response to the expressed enzyme. Subsequent challenge of the AAV2/DC190-alphagal-treated animals with recombinant human **alpha-galactosidase A** at 6 months failed to elicit the production of anti-**alpha-galactosidase A** antibodies, suggesting the induction of immune tolerance in these animals. The levels of expression attained with AAV2/DC190-alphagal in the Fabry mice were sufficient to reduce the abnormal accumulation of globotriaosylceramide in the liver, spleen, and heart to basal levels and in the kidney by approximately 40% at 8 weeks. Together, these results demonstrate that AAV2-mediated gene transfer that limits the expression of **alpha-galactosidase A** to the liver may be a viable strategy for treating **Fabry disease**.

L8 ANSWER 5 OF 27 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation. on STN

AU Park J; Murray G J; Limaye A; Quirk J M; Gelderman M P; Brady R O; Qasba P (Reprint)

TI Long-term correction of globotriaosylceramide storage in Fabry mice by recombinant adeno-associated virus-mediated gene transfer

SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (18 MAR 2003) Vol. 100, No. 6, pp. 3450-3454.
Publisher: NATL ACAD SCIENCES, 2101 CONSTITUTION AVE NW, WASHINGTON, DC 20418 USA.
ISSN: 0027-8424.

AB **Fabry disease** is an X-linked recessive inborn metabolic disorder characterized by systemic and vascular accumulation of globotriaosylceramide (Gb(3)) caused by a deficiency of the lysosomal enzyme **alpha-galactosidase A** (alpha-gal A). The condition is associated with an increased morbidity and mortality due to renal failure, cardiac disease, and early onset of stroke. Hemizygous males are primarily affected clinically with variable expression in heterozygous females. **Gene-therapy** trials have been initiated recently in alpha-gal A knockout mouse models of **Fabry disease** by using a variety of viral vectors. In the present investigation we administered single i.v. injections of 1 x 10(10) genomes of recombinant adeno-associated virus (rAAV) encoding the human alpha-gal A gene driven by a modified chicken beta-actin (CAG) promoter to alpha-gal A knockout (Fabry) mice. Transgenic mice were analyzed for expression of alpha-gal A activity and Gb(3) levels in liver, kidney, heart, spleen, small intestine, lung, and brain. Administration of the rAAV-CAG-hAGA vector resulted in stable expression of alpha-gal A in organs of the Fabry mice for >6 months. alpha-Gal A activity in the organs became equal to or higher than that of wild-type mice. Accumulated Gb(3) in the liver, heart, and spleen was reduced to that of wild-type mice with lesser but significant reductions in kidney, lung, and small intestine. Injection of the rAAV-CAG-hAGA construct into skeletal muscle did not result in expression of alpha-gal A in it or in other tissues. This study provides a basis for a simple and efficient **gene-therapy** approach for patients with **Fabry disease** and is indicative of its potential for the treatment of other lysosomal storage disorders.

L8 ANSWER 6 OF 27 MEDLINE on STN DUPLICATE 2

AU Mohrenschlager Matthias; Braun-Falco Markus; Ring Johannes; Abeck Dietrich

TI **Fabry disease**: recognition and management of cutaneous manifestations.

SO American journal of clinical dermatology, (2003) 4 (3) 189-96. Ref: 54
Journal code: 100895290. ISSN: 1175-0561.

AB **Fabry disease** (angiokeratoma corporis diffusum universale) is a rare, X chromosome-linked lysosomal storage disease. The

deficient enzyme, **alpha-galactosidase A** (alpha-gal A), is responsible for the accumulation of neutral glycosphingolipids within vascular endothelial lysosomes of various organs, including skin, kidneys, heart, and brain. The disease manifests primarily in affected hemizygous men and to some extent in heterozygous women ('carriers'). The diagnosis of **Fabry disease** is made in hemizygous males after the detection of the presence of angiokeratomas, irregularities in sweating, edema, scant body hair, painful sensations, and of cardiovascular, gastrointestinal, renal, ophthalmologic, phlebologic, and respiratory involvement. A deficiency of alpha-gal A in serum, leukocytes, tears, tissue specimens, or cultured skin fibroblasts further supports the diagnosis in male patients. Since heterozygous women show angiokeratomas in only about 30% of cases and may have alpha-gal A levels within normal range, genetic analysis is recommended. Current treatment of angiokeratomas of **Fabry disease** is based mainly on the use of laser systems, including variable pulse width 532nm Neodymium:Yttrium-Aluminum-Garnet (Nd:YAG) laser, 578nm copper vapor laser, and flashlamp-pumped dye laser. When cutaneous and mucous glands are affected, restrictions may be required with regard to the time spent in a warm climate and the amount time spent working or on sporting activities, and may necessitate the use of topical and systemic antiperspirant agents, and topical application of artificial lacrimal fluid and saliva, respectively. For the future, new treatment modalities, including **enzyme** replacement **therapy**, substrate deprivation strategies, and **gene therapy** offer extraordinary options for the cutaneous and visceral lesions in patients with **Fabry disease**.

L8 ANSWER 7 OF 27 MEDLINE on STN

AU Blom Daniel; Speijer Dave; Linthorst Gabor E; Donker-Koopman Wilma G; Strijland Anneke; Aerts Johannes M F G

TI Recombinant **enzyme therapy** for **Fabry disease**: absence of editing of human **alpha-galactosidase A** mRNA.

SO American journal of human genetics, (2003 Jan) 72 (1) 23-31. Journal code: 0370475. ISSN: 0002-9297.

AB For more than a decade, **protein**-replacement **therapy** has been employed successfully for the treatment of Gaucher disease. Recently, a comparable therapy has become available for the related lipid-storage disorder **Fabry disease**. Two differently produced recombinant **alpha-galactosidase A** (alpha-gal A) preparations are used independently for this purpose. Agalsidase alpha is obtained from human fibroblasts that have been modified by gene activation; agalsidase beta is obtained from Chinese hamster ovary cells that are transduced with human alpha-gal A cDNA. It has previously been claimed that alpha-gal A mRNA undergoes editing, which may result in coproduction of an edited protein (Phe 396 Tyr) that might have a relevant physiological function. We therefore analyzed the occurrence of alpha-gal A editing, as well as the precise nature, in this respect, of the therapeutic enzymes. No indications were obtained for the existence of editing at the protein or RNA level. Both recombinant **enzymes** used in **therapy** are unedited and are capable of functionally correcting cultured fibroblasts from Fabry patients in their excessive globotriaosylceramide accumulation. Although RNA editing is apparently not relevant in the case of alpha-gal A, a thorough analysis of the potential occurrence of editing of transcripts is nevertheless advisable in connection with newly developed **protein**-replacement **therapies**.

L8 ANSWER 8 OF 27 MEDLINE on STN DUPLICATE 3

AU Takahashi Hiroshi; Hirai Yukihiko; Migita Makoto; Seino Yoshihiko; Fukuda Yuh; Sakuraba Hitoshi; Kase Ryoichi; Kobayashi Toshihide; Hashimoto Yasuhiro; Shimada Takashi

TI Long-term systemic therapy of **Fabry disease** in a

knockout mouse by adeno-associated virus-mediated muscle-directed gene transfer.

SO Proceedings of the National Academy of Sciences of the United States of America, (2002 Oct 15) 99 (21) 13777-82.
Journal code: 7505876. ISSN: 0027-8424.

AB **Fabry disease** is a systemic disease caused by genetic deficiency of a lysosomal enzyme, **alpha-galactosidase A** (alpha-gal A), and is thought to be an important target for **enzyme** replacement **therapy**. We studied the feasibility of gene-mediated enzyme replacement for **Fabry disease**. The adeno-associated virus (AAV) vector containing the alpha-gal A gene was injected into the right quadriceps muscles of Fabry knockout mice. A time course study showed that alpha-gal A activity in plasma was increased to approximately 25% of normal mice and that this elevated activity persisted for up to at least 30 weeks without development of anti-alpha-gal A antibodies. The alpha-gal A activity in various organs of treated Fabry mice remained 5-20% of those observed in normal mice. Accumulated globotriaosylceramide in these organs was completely cleared by 25 weeks after vector injection. Reduction of globotriaosylceramide levels was also confirmed by immunohistochemical and electronmicroscopic analyses. Echocardiographic examination of treated mice demonstrated structural improvement of cardiac hypertrophy 25 weeks after the treatment. AAV vector-mediated muscle-directed gene transfer provides an efficient and practical therapeutic approach for **Fabry disease**.

L8 ANSWER 9 OF 27 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation. on STN

AU Schiffmann R (Reprint); Brady R O

TI New prospects for the treatment of lysosomal storage diseases

SO DRUGS, (FEB 2002) Vol. 62, No. 5, pp. 733-742.
Publisher: ADIS INTERNATIONAL LTD, 41 CENTORIAN DR, PRIVATE BAG 65901, MAIRANGI BAY, AUCKLAND 10, NEW ZEALAND.
ISSN: 0012-6667.

AB Although individually rare, lysosomal storage disorders constitute a significant burden on society. To date, **enzyme** replacement **therapy** (ERT) has been the most successful therapeutic approach for lysosomal storage disorders.

ERT reverses systemic manifestations of Gaucher disease but does not effectively treat the neurological complications. Recently, ERT produced a reduction of severe neuropathic pain, stabilisation of renal disease, and improved vascular function and structure in short-term, placebo-controlled trials in patients with Fabry's disease. Long-term studies are necessary to evaluate the full potential of ERT in this disease. In patients with Pompe disease, a fatal cardiac and skeletal muscle disorder, ERT improved cardiac function and structure, and increased overall muscle strength. It has already increased survival in a small number of affected infants. ERT also decreased liver and spleen size, joint mobility and quality of life in patients with mucopolysaccharidosis type I, but when the therapeutic protein is administered intravenously, it is unlikely to modify the neurological outcome in this or in other similar disorders.

Bone marrow transplantation continues to be effective in Gaucher disease, in some forms of mucopolysaccharidosis and in mild forms of Krabbe disease, but it has high morbidity and mortality that limits its use in lysosomal storage disorders. Drugs that slow the rate of formation of accumulating glycolipids are being developed and one of them, OGT-918 (N-butyldeoxynojirimycin), is showing promise in patients with Gaucher disease. **Gene therapy** for lysosomal storage disorders holds promise as a replacement for the other therapies described here but requires much more development before clinical efficacy trials.

L8 ANSWER 10 OF 27 MEDLINE on STN DUPLICATE 4

AU Peces R; Olea T

TI [**Fabry disease**: clinic and enzymatic diagnosis of

homozygous and heterozygous. New therapeutic prospects].
Enfermedad de Fabry: diagnostico clinico y enzimatico de homocigotos y heterocigotos. Nuevas perspectivas terapeuticas.

SO Nefrologia : publicacion oficial de la Sociedad Espanola Nefrologia, (2002) 22 (6) 540-6.
Journal code: 8301215. ISSN: 0211-6995.

AB **Fabry disease** is an X-linked recessive lysosomal storage disorder caused by a partial or complete deficiency of **alpha-galactosidase A**. Intracellular accumulation of globotriaosylceramide, the glycolipid substrate of this enzyme, leads to severe painful neuropathy with progressive renal, cardiovascular, and cerebrovascular dysfunction and early death. Men are predominantly affected but many female carriers have similar clinical involvement, including increased risk of stroke. Physical stigmata, such as angiokeratomas in skin and mucous membranes and characteristic benign corneal abnormalities, facilitate identification of **Fabry disease**. The finding of a marked decreased activity of (**alpha-galactosidase A** in plasma, white blood cells or cultured skin fibroblasts confirms the diagnosis. Treatment thus far has been symptomatic only. Etiology-based **therapies** are being developed that include **enzyme** replacement **therapy** , **gene therapy**, and substrate deprivation. The recently completed double-blind, placebo-controlled trials of intravenous infusions of (**alpha-galactosidase A** in patients with **Fabry disease** demonstrated the safety and efficacy of this treatment. We report a family with **Fabry disease** composed of hemicygous and heterocygous. The propositus developed chronic renal failure and received a cadaver renal transplant, which remained with adequate renal function during 15 years.

L8 ANSWER 11 OF 27 MEDLINE on STN
AU Pastores Gregory M; Thadhani Ravi
TI Advances in the management of Anderson-**Fabry disease**: **enzyme** replacement **therapy**.
SO Expert opinion on biological therapy, (2002 Mar) 2 (3) 325-33. Ref: 46
Journal code: 101125414. ISSN: 1471-2598.

AB Anderson-**Fabry disease** (AFD) is a lysosomal storage disorder (LSD) due to **alpha-galactosidase A** (alpha-Gal A) deficiency and the resultant accumulation of incompletely metabolised glycosphingolipids (GSLs), primarily globotriosylceramide (Gb(3)), within various tissues. It is an X-linked multisystem disorder characterised by progressive renal insufficiency, with added morbidity from cardio- and cerebrovascular involvement, and associated with significant impact on quality of life and diminished lifespan. The disease manifests primarily in hemizygous males; however, there is increasing recognition that heterozygous (carrier) females may also develop disease-related complications, although onset among affected women may be delayed. Until recently, treatment has been limited to symptomatic management of pain and other measures to alleviate the problems associated with end-stage complications from renal, cardiac and nervous system involvement. The availability of the recombinant enzyme offers the potential of a safe and effective targeted treatment approach. At the moment, two distinct enzyme formulations are approved in Europe (and in other countries) and both continue to undergo FDA evaluation in the US. Increasing knowledge of the natural history of AFD and greater experience with **enzyme therapy** should enable optimal patient care. The relative rarity and complexity of AFD necessitates a multi-disciplinary team approach that may be facilitated by a centralised registry.

L8 ANSWER 12 OF 27 MEDLINE on STN DUPLICATE 5
AU Germain Dominique P
TI [Fabry's disease (**alpha-galactosidase-A** deficiency): recent therapeutic innovations].

Maladie de Fabry (deficit en **alpha-galactosidase A**): innovations therapeutiques recentes.

SO Journal de la Societe de biologie, (2002) 196 (2) 183-90. Ref: 41
Journal code: 100890617. ISSN: 1295-0661.

AB **Fabry disease** (FD, OMIM 301500) is an X-linked inherited disorder of metabolism due to mutations in the gene encoding **alpha-galactosidase A**, a lysosomal enzyme. The enzymatic defect leads to the accumulation of neutral glycosphingolipids throughout the body, particularly within endothelial cells. Resulting narrowing and tortuosity of small blood vessels with endothelial dysfunction lead to tissue ischaemia and infarction. Inability to prevent the progression of glycosphingolipid deposition causes significant morbidity and mortality from early onset strokes, cardiomyopathy and renal failure in adulthood. Medical management is symptomatic and consists of partial pain relief with analgesic drugs (gabapentin, carbamazepine), antihypertensive drugs, whereas renal transplantation or dialysis is available for patients experiencing end-stage renal failure. However, the ability to produce high doses of **alpha-galactosidase A** in vitro has opened the way to preclinical studies in the mouse model, and to the development of the first clinical trials in patients with **Fabry disease**. **Enzyme** replacement **therapy** has recently been validated as a therapeutic agent for **Fabry disease** patients. Long term safety and efficacy of replacement therapy are currently being investigated. Substrate deprivation and **gene therapy** may also prove future alternative therapeutic options.

L8 ANSWER 13 OF 27 MEDLINE on STN

AU Stern Aaron S; Klotman Mary E; Ioannou Yiannis A; Burrow Christopher R; Wilson Patricia D; Klotman Paul E; Lipkowitz Michael S

TI Polarity of **alpha-galactosidase A** uptake by renal tubule cells.

SO Kidney international, (2002 Jan) 61 (1 Suppl) 52-5.
Journal code: 0323470. ISSN: 0085-2538.

AB Polarity of **alpha-galactosidase A** uptake by renal tubule cells.BACKGROUND: Congenital absence of alpha-galactosidase in **Fabry disease** leads eventually to renal failure. **Fabry disease** is an attractive candidate for **gene therapy**, but uptake mechanisms of the **enzyme** must be understood for it to be used in treating patients with **Fabry disease**.METHODS: Immortalized human renal epithelial cells from three regions of the tubule were grown in culture on collagen-coated Transwell filters and were incubated with recombinant alpha-galactosidase protein placed at either the luminal or basolateral side of the cells. Uptake into cells was measured, and kinetic studies were performed. Blocking experiments were done with mannose 6-phosphate.RESULTS: Uptake from the basolateral side of the filters predominated in all three cell types. Only in distal tubule cells was mannose 6-phosphate able to block uptake to any degree. The kinetic data reveal a high Km for both luminal and basolateral cell surfaces.CONCLUSIONS: These data suggest that to correct the renal phenotype in **Fabry disease**, high levels of the enzyme will be need to be delivered to kidney cells. This will likely best be achieved with local administration of a vector containing the transgene directly to the kidney.

L8 ANSWER 14 OF 27 CAPLUS COPYRIGHT 2005 ACS on STN

IN Meeker, David; Cheng, Seng H.

TI Combination **enzyme** replacement, **gene therapy** and small molecule therapy for lysosomal storage diseases

SO PCT Int. Appl., 45 pp.
CODEN: PIXXD2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI WO 2001097829 A2 20011227 WO 2001-US19579 20010619
WO 2001097829 A3 20021227
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AB This invention provides various combinations of **enzyme** replacement **therapy**, **gene therapy**, and small mol. therapy for the treatment of lysosomal storage diseases. **Therapy** include .**alpha**.-**galactosidase** **A enzyme** , deoxynorjirimycin derivs. (small mols.) for **Fabry disease**.

L8 ANSWER 15 OF 27 MEDLINE on STN DUPLICATE 6
AU Jung S C; Han I P; Limaye A; Xu R; Gelderman M P; Zerfas P; Tirumalai K; Murray G J; During M J; Brady R O; Qasba P
TI Adeno-associated viral vector-mediated gene transfer results in long-term enzymatic and functional correction in multiple organs of Fabry mice.
SO Proceedings of the National Academy of Sciences of the United States of America, (2001 Feb 27) 98 (5) 2676-81.
Journal code: 7505876. ISSN: 0027-8424.
AB **Fabry disease** is a lysosomal storage disorder caused by a deficiency of the lysosomal enzyme **alpha**-**galactosidase A** (alpha-gal A). This enzyme deficiency leads to impaired catabolism of alpha-galactosyl-terminal lipids such as globotriaosylceramide (Gb3). Patients develop painful neuropathy and vascular occlusions that progressively lead to cardiovascular, cerebrovascular, and renal dysfunction and early death. Although **enzyme** replacement **therapy** and bone marrow transplantation have shown promise in the murine analog of **Fabry disease**, **gene therapy** holds a strong potential for treating this disease in humans. Delivery of the normal alpha-gal A gene (cDNA) into a depot organ such as liver may be sufficient to elicit corrective circulating levels of the deficient enzyme. To investigate this possibility, a recombinant adeno-associated viral vector encoding human alpha-gal A (rAAV-AGA) was constructed and injected into the hepatic portal vein of Fabry mice. Two weeks postinjection, alpha-gal A activity in the livers of rAAV-AGA-injected Fabry mice was 20-35% of that of the normal mice. The transduced animals continued to show higher alpha-gal A levels in liver and other tissues compared with the untouched Fabry controls as long as 6 months after treatment. In parallel to the elevated enzyme levels, we see significant reductions in Gb3 levels to near normal at 2 and 5 weeks posttreatment. The lower Gb3 levels continued in liver, spleen, and heart, up to 25 weeks with no significant immune response to the virus or alpha-gal A. Also, no signs of liver toxicity occurred after the rAAV-AGA administration. These findings suggest that an AAV-mediated gene transfer may be useful for the treatment of **Fabry disease** and possibly other metabolic disorders.

L8 ANSWER 16 OF 27 MEDLINE on STN DUPLICATE 7
AU Estruch E J; Hart S L; Kinnon C; Winchester B G
TI Non-viral, integrin-mediated gene transfer into fibroblasts from patients with lysosomal storage diseases.
SO journal of gene medicine, (2001 Sep-Oct) 3 (5) 488-97.
Journal code: 9815764. ISSN: 1099-498X.
AB BACKGROUND: Non-viral vectors consisting of Lipofectin/integrin-targeting peptide/DNA (LID) complexes have great potential for **gene** **therapy**, as they are safe, simple, and able to package large DNA molecules. In this study, these vectors were evaluated in vitro for the

therapy of lysosomal storage disorders. METHODS: Non-viral vectors were designed to deliver therapeutic genes by integrin-mediated uptake into fibroblasts from patients with the lysosomal storage disorders fucosidosis and **Fabry disease**, which result from deficiencies of alpha-L-fucosidase and **alpha-galactosidase A**, respectively. The vectors consisted of a complex (LID) of Lipofectin and a peptide containing an integrin-targeting domain and a poly-lysine domain to which was bound plasmid DNA, containing alpha-L-fucosidase (LID-alpha-Fuc) or **alpha-galactosidase A** (LID-alpha-Gal). RESULTS: Patients' fibroblasts transfected with LID-alpha-Fuc and LID-alpha-Gal produced the corresponding enzyme at levels which were 10-40% of the total activity in cultures of normal fibroblasts. However, 95-98% of this activity was secreted. Transfection of endothelial cells, the main target cells in **Fabry disease**, with an LID-alpha-Gal produced a total alpha-galactosidase activity 65% higher than that in untransfected cultures after 6 days, 67% of the activity being secreted. Although transfection of fibroblasts with LID complexes also caused small changes in the distribution of endogenous lysosomal enzymes, it did not appear to affect the viability of the cells. CONCLUSIONS: The integrin-mediated transfer of genes encoding lysosomal enzymes into cells results in the secretion of large amounts of normal enzyme that could be taken up by other cells. This could be a useful strategy for **enzyme**-replacement **therapy**.

L8 ANSWER 17 OF 27 MEDLINE on STN
AU Desnick R J
TI Enzyme replacement and beyond.
SO Journal of inherited metabolic disease, (2001 Apr) 24 (2) 251-65. Ref: 64
Journal code: 7910918. ISSN: 0141-8955.
AB During the last decade, **enzyme** replacement **therapy** for lysosomal storage diseases became a reality with the demonstration of its safety and effectiveness in type 1 Gaucher disease. Currently, enzyme replacement and several other potential therapeutic strategies are being developed for selected lysosomal storage diseases, including **Fabry disease** due to the deficient activity of **alpha-galactosidase A** (alpha-Gal A). The development and clinical evaluation of these new therapies require a stepwise process, each step being rigorously reviewed and approved by national or international regulatory agencies. For lethal disorders that affect small populations, such as many inherited metabolic diseases, this process can be accelerated by 'orphan drug' and 'fast track' regulations. As an example of the drug development process, the development of recombinant human alpha-Gal A (r-halphaGal A) replacement for **Fabry disease** is presented, including the preclinical studies in the 'Fabry mouse' model, and the clinical phase 1/2, phase 3, and phase 3 extension studies, which demonstrate the safety and efficacy of this new therapy.

L8 ANSWER 18 OF 27 MEDLINE on STN DUPLICATE 8
AU MacDermot J; MacDermot K D
TI Neuropathic pain in Anderson-**Fabry disease**: pathology and therapeutic options.
SO European journal of pharmacology, (2001 Oct 19) 429 (1-3) 121-5. Ref: 30
Journal code: 1254354. ISSN: 0014-2999.
AB An inherited deficiency of the enzyme **alpha-galactosidase A** is manifest clinically as Anderson-**Fabry disease**. Most affected patients present with severe peripheral pain in childhood or early adult life, and frequently progress to multi-organ failure by the 4th or 5th decades. The present review examines the probable mechanisms that contribute to pain in these patients, and outlines some of the treatment options that are currently used. The successful outcome of the first two trials of **enzyme** replacement **therapy** suggest that this disease might be amenable

in the future to **gene therapy**.

L8 ANSWER 19 OF 27 MEDLINE on STN DUPLICATE 9
AU Siatskas C; Medin J A
TI **Gene therapy** for **Fabry disease**.
SO Journal of inherited metabolic disease, (2001) 24 Suppl 2 25-41; discussion 11-2. Ref: 105
Journal code: 7910918. ISSN: 0141-8955.
AB **Fabry disease** is an X-linked metabolic disorder caused by a deficiency of **alpha-galactosidase A** (alpha-Gal A). Lack of this lysosomal hydrolase results in the accumulation of galactose-terminal glycosphingolipids in a number of tissues, including vascular endothelial cells. Premature death is predominantly associated with vascular conditions of the heart, kidneys and brain. Historically, treatment has largely been palliative. Alternative treatments for many lysosomal storage diseases have been developed, including allogeneic organ and bone marrow transplantation, **enzyme** replacement **therapy**, and **gene therapy**. Significant clinical risks still exist with allogeneic transplantations. Alpha-Gal A **enzyme** replacement **therapy** has been implemented in clinical trials. This approach has been effective but may have limitations for long-term systemic or cost-effective correction. As an alternative, **gene therapy** approaches, involving a variety of gene delivery systems, have been pursued for the amelioration of **Fabry disease** . **Fabry disease** is a compelling disorder for **gene therapy**, as target cells are readily accessible and relatively low levels of enzyme correction may suffice to reduce storage. Importantly, metabolic cooperativity effects are also manifested in **Fabry disease**, wherein corrected cells secrete alpha-Gal A that can correct bystander cells. In addition, a broad therapeutic window probably exists, and mouse models of **Fabry disease** have been generated to assist studies. As an example, in vitro and in vivo studies using alpha-Gal A-transduced haematopoietic cells from Fabry mice have demonstrated enzymatic correction of recipient cells and dissemination of alpha-Gal A upon transplantation, leading to reduced lipid storage in a number of clinically relevant organs. This corrective enzymatic effect has recently been shown to be even further enhanced upon pre-selection of therapeutically transduced cells prior to transplantation. This review will briefly detail current gene delivery methods and summarize results to date in the context of **gene therapy** for **Fabry disease**.

L8 ANSWER 20 OF 27 CAPLUS COPYRIGHT 2005 ACS on STN
IN Yew, Nelson S.; Ziegler, Robin J.; Cheng, Seng H.
TI Compositions and methods for treating lysosomal storage disease
SO PCT Int. Appl., 54 pp.
CODEN: PIXXD2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000009153	A1	20000224	WO 1998-US22886	19981029
W: AU, CA, IL, JP				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2305768	AA	20000224	CA 1998-2305768	19981029
AU 9912847	A1	20000306	AU 1999-12847	19981029
AU 734290	B2	20010607		
US 6066626	A	20000523	US 1998-182245	19981029
EP 1027069	A1	20000816	EP 1998-956290	19981029
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002522509	T2	20020723	JP 2000-564655	19981029
US 2003087868	A1	20030508	US 2002-244700	20020913

AB The present invention provides recombinant viral and non-viral vectors

comprising a transgene encoding a biol. active human lysosomal enzyme that are able to infect and/or transfect and sustain expression of the biol. active human lysosomal enzyme transgene in mammalian cells deficient therein. In addition, methods are provided for providing a biol. active human lysosomal enzyme to cells deficient therein, which comprises introducing into the cells a vector comprising and expressing a transgene encoding the biol. active human lysosomal enzyme, wherein the vector is taken up by the cells, the transgene is expressed and biol. active enzyme is produced. The cells may be infected and/or transfected by the vector, dependent upon whether the vector is a viral vector and/or plasmid or the like. The invention also provides a method of supplying a biol. active human lysosomal enzyme to other distant cells deficient therein wherein the transfected and/or infected cells harboring the vector secrete the biol. active enzyme which is then taken up by the other deficient cells. In a preferred embodiment the present invention provides for sustained production of biol. human active .**alpha**.-**galactosidase** **A** in cells of Fabry individuals that are deficient in said enzyme.

L8 ANSWER 21 OF 27 CAPLUS COPYRIGHT 2005 ACS on STN

IN Selden, Richard F.; Borowski, Marianne; Gillispie, Frances P.; Kinoshita, Carol M.; Treco, Douglas A.; Williams, Melanie D.

TI Gene and **enzyme** replacement **therapy** for .**alpha**.-**galactosidase** **A** deficiency

SO U.S., 32 pp.
CODEN: USXXAM

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6083725	A	20000704	US 1997-928881	19970912
US 6458574	B1	20021001	US 1999-266014	19990311
US 6566099	B1	20030520	US 2000-491759	20000127
US 6395884	B1	20020528	US 2000-543921	20000406
AU 762400	B2	20030626	AU 2001-93403	20011123
US 2003077806	A1	20030424	US 2002-165060	20020607
US 2003113894	A1	20030619	US 2002-165968	20020610
US 2003152560	A1	20030814	US 2002-318905	20021212

AB A therepeutic method whereby an individual suspected of having an .**alpha**.-**galactosidase** **A** deficiency, such as **Fabry** **disease**, is treated either with (1) human cells that have been genetically modified to overexpress and secrete human α-gal A, or (2) purified human α-gal A obtained from cultured, genetically modified human cells. A therapeutic method is provided whereby an individual suspected of having an .**alpha**.-**galactosidase** **A** (α-gal A) deficiency, such as **Fabry** **disease**, is treated either with (1) human cells that have been genetically modified to overexpress and secrete human α-gal A, or (2) purified human α-gal A obtained from cultured, genetically modified human cells. Expressing a DNA encoding human α-gal A in cultured human cells produces a polypeptide that is glycosylated appropriately, so that it is not only enzymically active and capable of acting on the glycosphingolipid substrate which accumulates in **Fabry** **disease**, but is also efficiently internalized by cells via cell surface receptors which target it exactly to where it is needed in this disease. Two expression plasmids, pXAG-16 and pXAG-28, were constructed. These plasmids contain human α-gal A cDNA encoding the 398 amino acids of the α-gal A enzyme (without its signal peptide); the human growth hormone (hGH) signal peptide genomic DNA sequence, which is interrupted by the first intron of the hGH gene; and the 3'-untranslated sequence (UTS) of the hGH gene, which contains a signal for polyadenylation. Plasmid pXAG-16 has the human cytomegalovirus immediate-early promoter and first intron (flanked by noncoding exon sequences), whereas pXAG-28 is driven by the collagen Iα2 promoter and also contains the β-actin gene's 5'-UTS, which contains the first intron of the β-actin gene. Expression by fibroblasts stably transfected with pXAG-16 or pXAG-28, using the hGH signal peptide, was

substantially higher than that in transfected fibroblasts using the homologous α-gal A signal peptide. Recombinant α-gal A could be purified by Butyl-Sepharose hydrophobic interaction chromatog., heparin-Sepharose chromatog., hydroxylapatite chromatog., Q Sepharose HP anion-exchange chromatog., and Superdex-200 gel filtration chromatog. Purified α-Gal A activity was stable over a 3-mo period when the pH of the formulation was <6.5.

L8 ANSWER 22 OF 27 MEDLINE on STN DUPLICATE 10
AU Brady R O; Schiffmann R
TI Clinical features of and recent advances in therapy for **Fabry disease**.
SO JAMA : journal of the American Medical Association, (2000 Dec 6) 284 (21) 2771-5.
Journal code: 7501160. ISSN: 0098-7484.
AB **Fabry disease** is an X-linked recessive lysosomal storage disorder caused by a deficiency of **alpha-galactosidase A**. Intracellular accumulation of globotriaosylceramide, the glycolipid substrate of this enzyme, leads to severe painful neuropathy with progressive renal, cardiovascular, and cerebrovascular dysfunction and early death. Men are predominantly affected but many female carriers have similar clinical involvement, including increased risk of stroke. Physical stigmata, such as angiokeratomas in skin and mucous membranes and characteristic benign corneal abnormalities, facilitate identification of **Fabry disease**. The finding of a marked decreased activity of **alpha-galactosidase A** in white blood cells or cultured skin fibroblasts confirms the diagnosis. Treatment thus far has been symptomatic only. Etiology-based **therapies** are being developed that include **enzyme** replacement **therapy**, **gene therapy**, and substrate deprivation. Our recently completed double-blind, placebo-controlled trial of intravenous infusions of **alpha-galactosidase A** in patients with **Fabry disease** demonstrated the safety and efficacy of this treatment. JAMA. 2000;284:2771-2775.

L8 ANSWER 23 OF 27 MEDLINE on STN
AU Linthorst G E; Hollak C E; Bosman D K; Heymans H S; Aerts J M
TI [Fabry's disease; towards a treatment].
De ziekte van Fabry: op weg naar een behandeling.
SO Nederlands tijdschrift voor geneeskunde, (2000 Dec 9) 144 (50) 2391-5.
Ref: 28
Journal code: 0400770. ISSN: 0028-2162.
AB Fabry's disease, deficiency of the enzyme **alpha-galactosidase A**, is an X-linked lysosomal storage disorder. Clinical symptoms are caused by continuous deposition of specific glycolipids in endothelial cells, neural cells, skin and cornea. These depositions give rise to skin (angiokeratoma) and eye abnormalities (cornea verticillata), acroparaesthesias and anhidrosis and later in life cause renal insufficiency and cardiovascular complications. Hemizygous males suffer from Fabry's disease, whereas female carriers (heterozygotes) are usually asymptomatic. Recently, an atypical presentation of Fabry's disease was described in males who only presented with cardiac involvement. Therefore, the actual number of Fabry patients in the Netherlands could be higher than the predicted 300. Diagnosis in males can be established by measuring alpha-galactosidase enzyme activity in plasma, leukocytes or fibroblasts. Apart from kidney transplantation only symptomatic therapy is available today. **Enzyme** supplementation **therapy** (as shown in Gaucher's disease) and substrate deprivation are possible ways of treatment in the future.

L8 ANSWER 24 OF 27 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN
AU Shimada, T. [Reprint author]; Takahashi, H. [Reprint author]; Hirai, Y.

[Reprint author]; Takahashi, K. [Reprint author]; Migita, M. [Reprint author]; Kase, R.; Sakuraba, H.

TI Efficient enzymatic cross-correction of Fabry patients fibroblasts by adeno-associated virus vector mediated transfer of the **alpha-galactosidase A** gene.

SO Journal of Inherited Metabolic Disease, (July, 2000) Vol. 23, No. Supplement 1, pp. 224. print.
Meeting Info.: VIIIth International Conference on Inborn Errors of Metabolism. England, Cambridge, UK. September 13-17, 2000.
CODEN: JIMDDP. ISSN: 0141-8955.

L8 ANSWER 25 OF 27 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation. on STN

AU Ohsugi K; Kobayashi K; Itoh K; Sakuraba H; Sakuragawa N (Reprint)

TI Enzymatic corrections for cells derived from **Fabry disease** patients by a recombinant adenovirus vector

SO JOURNAL OF HUMAN GENETICS, (1 JAN 2000) Vol. 45, No. 1, pp. 1-5.
Publisher: SPRINGER-VERLAG TOKYO, 3-3-13, HONGO, BUNKYO-KU, TOKYO 113, JAPAN.
ISSN: 1434-5161.

AB **Fabry disease** is an X-linked inherited metabolic disorder caused by a deficiency of alpha-galactosidase (alpha-gal), resulting in the accumulation of ceramide trihexoside (CTH) in body fluids and in many organs and tissues. We constructed a recombinant adenovirus with a human alpha-gal cDNA (AxCAG alpha-gal), and transfected this vector to skin fibroblasts from Fabry patients. Transfected cells expressed high amounts of alpha-gal in their cytoplasm, and a high level of alpha-gal activity was detected in the medium. The accumulated CTH in the fibroblasts disappeared 3 days after infection. The secreted alpha-gal also eliminated the accumulated CTH from uninfected patient's cells. The enzyme may be taken up through mannose-6-phosphate receptors, as the addition of mannose-6-phosphate to the medium completely inhibited the uptake of the enzyme. The infected cells continued to express alpha-gal for more than 10 days. These results suggest that AxCAG alpha-gal could be used as **enzyme** replacement **gene therapy** for **Fabry disease**.

L8 ANSWER 26 OF 27 CAPLUS COPYRIGHT 2005 ACS on STN

IN Selden, Richard F.; Borowski, Marianne; Gillespie, Frances P.; Kinoshita, Carol M.; Treco, Douglas A.; Williams, Melanie D.

TI Gene and **enzyme** replacement **therapy** for .**alpha**.-**galactosidase A** deficiency

SO PCT Int. Appl., 78 pp.
CODEN: PIXXD2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9811206	A2	19980319	WO 1997-US16603	19970912
WO 9811206	A3	19980813		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2265464	AA	19980319	CA 1997-2265464	19970912
AU 9744244	A1	19980402	AU 1997-44244	19970912
EP 935651	A2	19990818	EP 1997-942567	19970912
EP 935651	B1	20041229		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
CN 1230220	A	19990929	CN 1997-197909	19970912
NZ 334721	A	20010126	NZ 1997-334721	19970912

JP 2001504324	T2	20010403	JP 1998-514004	19970912
RU 2179034	C2	20020210	RU 1999-107287	19970912
NZ 506214	A	20021126	NZ 1997-506214	19970912
US 6458574	B1	20021001	US 1999-266014	19990311
NO 9901225	A	19990510	NO 1999-1225	19990312
AU 762400	B2	20030626	AU 2001-93403	20011123
US 2003077806	A1	20030424	US 2002-165060	20020607
US 2003113894	A1	20030619	US 2002-165968	20020610

AB A therapeutic method is provided whereby an individual suspected of having an .**alpha**.-**galactosidase A** (α-gal A) deficiency, such as **Fabry disease**, is treated either with (1) human cells that have been genetically modified to overexpress and secrete human α-gal A, or (2) purified human α-gal A obtained from cultured, genetically modified human cells. Expressing a DNA encoding human α-gal A in cultured human cells produces a polypeptide that is glycosylated appropriately, so that it is not only enzymically active and capable of acting on the glycosphingolipid substrate which accumulates in **Fabry disease**, but is also efficiently internalized by cells via cell surface receptors which target it exactly to where it is needed in this disease. Two expression plasmids, pXAG-16 and pXAG-28, were constructed. These plasmids contain human α-gal A cDNA encoding the 398 amino acids of the α-gal A enzyme (without its signal peptide); the human growth hormone (hGH) signal peptide genomic DNA sequence, which is interrupted by the first intron of the hGH gene; and the 3'-untranslated sequence (UTS) of the hGH gene, which contains a signal for polyadenylation. Plasmid pXAG-16 has the human cytomegalovirus immediate-early promoter and first intron (flanked by noncoding exon sequences), whereas pXAG-28 is driven by the collagen Iα2 promoter and also contains the β-actin gene's 5'-UTS, which contains the first intron of the β-actin gene. Expression by fibroblasts stably transfected with pXAG-16 or pXAG-28, using the hGH signal peptide, was substantially higher than that in transfected fibroblasts using the homologous α-gal A signal peptide. Recombinant α-gal A could be purified by Butyl-Sepharose hydrophobic interaction chromatog., heparin-Sepharose chromatog., hydroxylapatite chromatog., Q Sepharose HP anion-exchange chromatog., and Superdex-200 gel filtration chromatog. Purified α-Gal A activity was stable over a 3-mo period when the pH of the formulation was <6.5.

L8 ANSWER 27 OF 27 CAPLUS COPYRIGHT 2005 ACS on STN

AU Eng, Christine M.; Ashley, Grace A.; Burgert, Tania S.; Enriquez, Annette L.; D'souza, Marcus; Desnick, Robert J.

TI **Fabry disease**: thirty-five mutations in the .**alpha**.-**galactosidase A** gene in patients with classic and variant phenotypes

SO Molecular Medicine (New York) (1997), 3(3), 174-182
CODEN: MOMEF3; ISSN: 1076-1551

AB **Fabry disease**, an X-linked inborn error of glycosphingolipid catabolism, results from mutations in the .**alpha**.-**galactosidase A** (α-Gal A) gene located at Xq22.1. To determine the nature and frequency of the mol. lesions causing the classical and milder variant Fabry phenotypes and for precise carrier detection, the α-Gal A lesions in 42 unrelated Fabry hemizygotes were determined Genomic DNA was isolated from affected probands and their family members. The seven .**alpha**.-**galactosidase A** exons and flanking intronic sequences were PCR amplified and the nucleotide sequence was determined by solid-phase direct sequencing. Two patients with the mild cardiac phenotype had missense mutations, 191T and F113L, resp. In 38 classically affected patients, 33 new mutations were identified including 20 missense (M1T, A31V, H46R, Y86C, L89P, D92Y, C94Y, A97V, R100T, Y134S, G138R, A143T, S148R, G163V, D170V, C202Y, Y216D, N263S, W287C, and N298S), two nonsense (Q386X, W399X), one splice site mutation (IVS4 + 2T → C), and eight small exonic insertions or deletions (304del1, 613del9, 777del1, 1057del2, 1074del2, 1077del1,

1212del3, and 1094ins1), which identified exon 7 as a region prone to gene rearrangements. In addition, two unique complex rearrangements consisting of contiguous small insertions and deletions were found in exons 1 and 2 causing L45R/H46S and L120X, resp. These studies further define the heterogeneity of mutations causing **Fabry disease**, permit precise carrier identification and prenatal diagnosis in these families, and facilitate the identification of candidates for **enzyme** replacement **therapy**.